PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 27 April 2000 (27.04.00)	
International application No.: PCT/EP99/02745	Applicant's or agent's file reference: G67708 LF/mg
International filing date: 23 April 1999 (23.04.99)	Priority date: 20 October 1998 (20.10.98)
Applicant: FALCIANI, Marco et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

18 November 1999 (18.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FRIGNOLI, Luigi
Ing. A. Giambrocono & C. s.r.l.
Via Rosolino Pilo, 19/B
I-20129 Milano
ITALIE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	03.01.2001
Applicant's or agent's file reference G67708 LF/gf	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/02745	23/04/1999	20/10/1998

Applicant
ACS DOBFAR S.P.A et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Loeper, S Tel.+49 89 2399-2569

Form PCT/IPEA/416 (July 1992)

BAG FOR PRESERVING AND TRANSPORTING STERILE PRODUCTS IN POWDER FORM AND FOR FORMING SOLUTIONS OF SAID PRODUCTS IN THE BAG

The invention relates to a bag able to preserve a product in powder form under sterile conditions and to enable a liquid to be fed into the bag to form therein a sterile solution (this term also including a dispersion or suspension) of said product.

Many products obtained in sterile form in the solid state are known to be used in the liquid state as sterile solutions, suspensions, dispersions or the like.

A typical example is a pharmaceutical product such as an antibiotic or vitamin, or a culture medium for micro-organisms such as cells, bacteria or moulds which at the moment of use is dissolved or dispersed in liquid.

The problem of dissolving or dispersing a sterile powder in liquid while maintaining sterility is considerable and costly, and is solved in various ways, all involving problems which are summarized below by referring to two particularly important cases.

For example, cell culture medium is produced in the form of powder which can be sold as such in polyethylene bags or bottles closed with a screw stopper. To be used, this product is dissolved in liquid to form a solution (typically an amino acid, electrolyte or vitamin solution) in a totally aseptic environment, this involving time and considerable cost.

The sterile solution obtained in this manner is fed into a glass

jar or bottle in a suitable sterile bottling environment, and the sealed bottle is despatched to the client in a special housing and protection container. The user has then to open the bottle under aseptic conditions to be able to then withdraw the solution contained in it.

This method is well known, and is explained for example in lines 9-59 of column 1 of the patent US-A-4,910,147.

To solve these problems, US-A-4,910,147 proposes to sell to the user not the product, but instead an already prepared sterile solution of the cell culture medium enclosed in a sealed flexible bag, into which the solution is fed using semi-automatic aseptic filling machines. Such bags, which are completely filled with the solution, are much more manageable than glass bottles and can be easily and economically despatched by the producer to the user who, without the need for special apparatus or a sterile environment, can directly withdraw all or part of the sterile solution through one or more ports with which the bag is provided.

However, this system also presents problems because although it is relatively simple to store and transport small bags filled with liquid, in the case of bags containing a relatively large liquid volume, for example five litres or more, the hydraulic force exerted by the liquid during transport can break the bag, as is clearly explained in lines 34-50 of column 1 of US-A-4,968,642 which names the same inventors and the same proprietor as US-A-4,910,147.

For this reason US-A-4,968,624 describes a very complex rigid structure within which the bags containing the solutions have to be enclosed for their storage and transport.

Again for example, reference can be made to the method of using those sterile crystalline antibiotics (in powder form) contained in single-dose form in glass bottles sealed by rubber plugs. To use such antibiotics, using a syringe a sterile solvent (water) is

(preferably high density polyethylene) or polyvinyl chloride, the intermediate layer is constructed of a barrier material (preferably aluminium), and the outer layer is constructed of polyolefin, nylon or polyester.

The packaging of the bag 1 in the bags 11 and 12 is known, and is of the type illustrated in US-A-4,700,838, corresponding to EP-B-201880.

The nature of the barrier material in its general terms (additional to aluminium) can be as defined in US-A-4,910,147.

When the sterile product in powder form is to be used, the bag 1 is removed from the protection bags, the stopper 8 is unscrewed, and into the port 2 a perfuser is inserted so that its free end 16 fractures the membrane 6 (Figure 4). The perfuser is a well known device and will not be described for simplicity. Its end sealedly engages the cavity in the appendix 2, through which the desired quantity of water can be easily fed under sterile conditions into the bag 1 to form with the powdered product a solution 17 which fills only a part of the bag capacity. This merely partial filling of the bag 1 is necessary to enable the liquid in the bag to be energetically shaken in order to quickly and completely dissolve, disperse or suspend the product in powder form to make it suitable for use.

One of the preferred uses of the described bag is to preserve and transport sterile crystalline antibiotics and to form injectable solutions thereof in hospitals and the like.

To give a detailed practical example, a bag 1 is prepared from a sheet of low density polyethylene of 150 micron thickness, the bag having a height of 35 cm and a width of 45 cm. 300 g of an antibiotic in powder form are fed into this bag and preserved in a sterile environment. The bag 1 is sealed within an intermediate bag of high density polyethylene of 100 micron thickness, having a height of 40 cm and a width of 48 cm. The intermediate bag is

then inserted into and sealed inside an outer bag of 43 cm height and 54.4 cm width formed from three layers joined together, the inner layer being formed of high density polyethylene of 0.075 mm thickness, the intermediate layer being formed of a sheet of aluminium of 0.01 mm thickness, and the outer layer being of polyester resin of 0.012 mm thickness.

When the antibiotic is to be used, the inner bag 1 is removed from the intermediate bag 11 and outer bag 12 and 3000 ml of injection-quality water are fed into it via the described perfuser (Figure 4) to form a solution of the required concentration for the particular therapeutic dose, in this case 100 mg/ml. It is important to note that the antibiotic solution 17 occupies only a part of the bag capacity to enable the antibiotic to be quickly and completely dissolved by vigorously shaking the bag. The bag capacity is preferably between 1.5 and 2 times the volume of the solution to be prepared in it.

The antibiotic solution obtained in this manner can be used directly, for example it can be transferred into sterile syringes each containing 30 ml of solution. The syringes can be filled in groups (for example 10, 20 or more syringes at a time) by automatic machines of known type which withdraw the solution through the free end 16 of the perfuser (by arranging the bag with the port 2 pointing downwards) used for feeding the liquid into the bag.

If desired, individual doses of the antibiotic solution can be withdrawn through the port 4 (the presence of which is not strictly necessary but is preferred). To do this, the stopper 9 is removed, and a rubber plug 20 (which seals that part of the cavity of the port 4 external to the bag 1) and the membrane 7 are perforated by the syringe needle.

When the syringe needle is removed, the solution is unable to flow from the bag 1, this being prevented by the rubber plug 20.

If the syringes are not used within a short time after their filling, they can be preserved in a freezer and then be despatched to the user in hospital in controlled temperature containers.

From the aforegoing description it is apparent that the antibiotic solution can be very easily and quickly formed at the desired concentration in a sterile environment, and that syringes can then be filled likewise easily and economically.

By proceeding in the aforedescribed manner, very important advantages are obtained compared with traditional systems in that it is no longer necessary to preserve the sterile antibiotic in powder form in glass bottles, a considerable reduction in the risk of contamination of the final pharmaceutical product is achieved (with the traditional system, for each syringe the solution has to be prepared individually and be fed into the syringe in environments which are generally not sterile), and there is a considerable cost and ecological saving consequent on the fact that it is no longer necessary to use glass bottles, metal rings, rubber plugs (one for each bottle), glass vials for solvents, etc.

All this leads to a considerable cost reduction, especially because a large number of specialized personnel are no longer required for preparing the individual antibiotic solutions, this being a very costly operation in hospitals or in those places in which a large quantity of antibiotic solutions has to be prepared.

Very considerable advantages are obtained even if the sterile products contained in the bags are not pharmaceutical products but are other products in powder form to be dissolved or dispersed in various liquids for their use, such as cell culture media.

In addition to the described bag, the invention also relates to the method for preserving and transporting sterile products in powder form and for dissolving or dispersing them in liquids under sterile conditions, as defined in the introductory part and in the claims accompanying this description.

Claims:

1. A bag for preserving and transporting sterile products in powder form and for forming solutions, dispersions or suspensions of said products therein, the bag being of polyolefin construction, being hermetically sealed at its periphery and having at least one port also of polyolefin construction defining a passageway the two ends of which open inside and respectively outside the bag, said passageway being closed by a breakable membrane forming part of the port and ensuring the maintaining of sterility within the bag, characterised in that the bag contains a sterile product in powder form, the bag capacity exceeding the directly usable volume of the final sterile product solution, dispersion or suspension obtained by feeding a liquid into the bag through said port and said membrane.

2. A bag as claimed in claim 1, characterised in that said polyolefin is low density polyethylene.

3. A bag as claimed in claims 1 and 2, characterised by being enclosed and sealed within an intermediate bag also constructed of polyolefin and inserted into and sealed within an outer bag composed of three layers of different materials bonded together, and of which the inner layer is of polyolefin or polyvinyl chloride, the intermediate layer is of a barrier material, and the outer layer is of polyolefin, nylon or polyester.

4. A method for preserving and transporting sterile products in powder form and for forming solutions, dispersions or suspensions of said products, characterised in that said products are enclosed and sealed within a sterile bag constructed of flexible material and provided with apertures closed by membranes through which a liquid can be fed into the bag, the minimum capacity of the bag being at least 1.5 times the total volume of the liquid plus the powder fed into the bag.

NEW

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REC'D 05 JAN 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference G67708 LF/gf	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/02745	International filing date *(day/month/year)* 23/04/1999	Priority date *(day/month/year)* 20/10/1998
International Patent Classification (IPC) or national classification and IPC A61J1/00		
Applicant ACS DOBFAR S.P.A et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 13 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/11/1999	03.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Damiani, A Telephone No. +49 89 2399 2535

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/02745

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

5	as originally filed			
1,2,6-8	as received on	15/02/2000	with letter of	14/02/2000
3a-3c,3e-3g	as received on	22/11/2000	with letter of	21/11/2000

Claims, No.:

1-5	as received on	22/11/2000	with letter of	21/11/2000

Drawings, No.:

1-5	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
   see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Section V:

1). Relevant documents

Reference is made to the following documents:

D1: US 5 484 431

D2: US 5 364 384

2). Claim 1

The present application does not meet all the criteria listed in Article 33 (1) PCT, because the subject-matter of independent claim 1 does not involve an inventive step within the meaning of Article 33 (3) PCT.

2.1). Document D1 discloses a bag for preserving and transporting soluble sterile products in powder form (see *column 4, line 17*) and suitable for forming therein solutions with predetermined concentrations of said products. The bag is made out of polyolefins (see *column 4, line 8*). It is hermetically sealed and includes at least one port (see *column 2, line 30*), defining a passageway, the two ends of which open inside and respectively outside the bag. The bag contains an amount of product in powder form (see *column 4, line 17*), said amount[1] being surely apt to give a solution with the desired predetermined concentration. The total volume[2] of the final solution is certainly a multiple of single volumes of individual doses of the same solution.

2.2). It can be concluded that document D1, which is considered to represent the most relevant state of the art, discloses a bag from which the subject-matter of claim 1 differs merely in the following independent differentiating features:

a) the port(s) is/are made out of polyolefin construction;

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[1] This feature of the subject-matter (bag+powder) is defined by means of a value (desired predetermined concentration) which is not defined. It is always possible to determine a "concentration" which, by completely filling the bag as in document D1, will require exactly the same amount of product in powder form as claimed in claim 1.

[2] This feature of the subject-matter (bag+powder) is defined by means of a value (individual doses) which is not defined. It is always possible to extract, out of the bag as in document D1, individual doses, whose volume is submultiple of exactly the total volume of the final solution as claimed in claim 1.

b) the passageway is closed by a pierceable membrane for the introduction of a solvent into the bag and respectively for the withdrawal of the solution therefrom;
c) the solution only partially fills the bag capacity.

2.2.a). With reference to the first differentiating feature (a), it is evident that the choice of a well-known class of materials represents no invention, taking also into account that polyolefins are widely used in the technical field to which the present application refers.

2.2.b). With reference to the second differentiating feature (b), the problem to be solved may be regarded as providing a more effective hermetic seal to the bag during storage and transportation.

The solution, which involves the introduction in the port of a pierceable membrane, proposed in claim 1 of the present application, is immediately suggested by document D2 (see *column 3, lines 33-38*). It would be obvious to the person skilled in the art, namely when the same effect of a sterile seal is to be achieved, to apply a pierceable membrane to the port of the bag described in document D1.

2.2.c). The third differentiating feature (c), is clearly shown by document D2 (see filling level of solution chamber [22] in *Fig. 1-3*).

2.3). It can be concluded that the skilled man, by combining independently all three features (a), (b) and (c) to the bag according to document D1, would immediately arrive at the bag according to claim 1 without having performed any inventive step.

3). Claim 3
Also the subject-matter of independent claim 3 does not involve an inventive step within the meaning of Article 33 (3) PCT.

3.1). Document D1 discloses a bag constructed of polyolefin material (see *column 4, line 8*) and containing a ready to use solution prepared by introducing within a sealed bag originally containing a dosed amount of a soluble sterile product in powder form (see

column 4, line 17) an amount[3] of solvent apt to give said ready to use solution with desired concentration of said product. The total volume[4] of said solution is a multiple of single volumes of individual doses of the same solution.

3.2). It can be concluded that document D1, which is considered to represent the most relevant state of the art, discloses a bag from which the subject-matter of claim 3 differs merely in that:
- the solution only partially fills the bag capacity.

This feature is clearly shown by document D2 (see filling level of solution chamber [22] in *Fig. 1-3*).

3.3). It can be concluded that the skilled man, by combining this feature to the bag according to document D1, would immediately arrive at the bag according to claim 3 without having performed any inventive step.

4). Dependent claims 2 and 4

Claims 2 and 4 show additional features, which, in combination with the features of the non-inventive claims to which they refer, lead to subject-matters that are also not inventive within the meaning of Article 33 (3) PCT.

The skilled man would reach same values (1.5 to 2) of the ratio between bag capacity total volume of the solution by means of a limited number of standard tests, without therefore having performed any inventive step.

5). Claim 5

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[3] This feature of the subject-matter (bag+powder+solvent) is defined by means of a value (desired concentration) which is not defined. It is always possible to determine a certain "concentration" which, by completely filling the bag as in document D1, will require exactly the same amount of solvent as claimed in claim 3.

[4] This feature of the subject-matter (bag+powder) is defined by means of a value (individual doses) which is not defined. It is always possible to extract, out of the bag as in document D1, individual doses, whose volume is submultiple of exactly the total volume of the final solution as claimed in claim 3.

Also the subject-matter of independent claim 5 does not involve an inventive step within the meaning of Article 33 (3) PCT.

5.1). Document D1 discloses a method for preparing solutions with predetermined concentrations of soluble sterile products in powder form (see *column 4, line 17*) enclosed and sealed within sterile bags constructed of flexible polyolefin materials (see *column 4, line 8*). A bag containing a dosed amount of soluble sterile product in powder form (see *column 4, line 17*) adapted to give a solution of predetermined concentration is fed with an amount[5] of solvent apt to give a ready to use solution with the desired concentration of the product. The volume[6] of the solution suffices to supply a plurality of single individual doses of the same solution.

5.2). It can be concluded that document D1, which is considered to represent the most relevant state of the art, discloses a bag from which the subject-matter of claim 5 differs merely in that:
- the solution only partially fills the bag capacity.

This feature is clearly shown by document D2 (see filling level of solution chamber [22] in *Fig. 1-3*).

5.3). It can be concluded that the skilled man, by combining this feature to the method according to document D1, would immediately arrive at the method according to claim 5 without having performed any inventive step.

6). Industrial applicability
The subject-matter of claims 1-5 is undoubtedly industrially applicable (Article 33 (4) PCT).

Section VII:

[5] This feature is defined by means of a value (desired concentration) which is not defined.

[6] This feature is defined by means of a value (individual doses) which is not defined.

1). Contrary to the prescriptions of Rule 6.2 (b) PCT, the technical features mentioned in the claims are not followed by the reference signs relating to such features in the drawings.

BAG FOR PRESERVING AND TRANSPORTING STERILE PRODUCTS IN POWDER FORM AND FOR FORMING SOLUTIONS OF SAID PRODUCTS IN THE BAG

The invention relates to a bag able to preserve a product in powder form under sterile conditions and to enable a liquid to be fed into the bag to form therein a sterile solution ~~/(this term also including a dispersion or suspension)/~~ of said product.

Many products obtained in sterile form in the solid state are known to be used in the liquid state as sterile solutions, suspensions, dispersions or the like.

A typical example is a pharmaceutical product such as an antibiotic or vitamin, or a culture medium for micro-organisms such as cells, bacteria or moulds which at the moment of use is dissolved or dispersed in liquid.

The problem of dissolving or dispersing a sterile powder in liquid while maintaining sterility is considerable and costly, and is solved in various ways, all involving problems which are summarized below by referring to two particularly important cases.

For example, cell culture medium is produced in the form of powder which can be sold as such in polyethylene bags or bottles closed with a screw stopper. To be used, this product is dissolved in liquid to form a solution (typically an amino acid, electrolyte or vitamin solution) in a totally aseptic environment, this involving time and considerable cost.

The sterile solution obtained in this manner is fed into a glass

jar or bottle in a suitable sterile bottling environment, and the sealed bottle is despatched to the client in a special housing and protection container. The user has then to open the bottle under aseptic conditions to be able to then withdraw the solution contained in it.

This method is well known, and is explained for example in lines 9-59 of column 1 of the patent US-A-4,910,147.

To solve these problems, US-A-4,910,147 proposes to sell to the user not the product, but instead an already prepared sterile solution of the cell culture medium enclosed in a sealed flexible bag, into which the solution is fed using semi-automatic aseptic filling machines. Such bags, which are completely filled with the solution, are much more manageable than glass bottles and can be easily and economically despatched by the producer to the user who, without the need for special apparatus or a sterile environment, can directly withdraw all or part of the sterile solution through one or more ports with which the bag is provided.

However, this system also presents problems because although it is relatively simple to store and transport small bags filled with liquid, in the case of bags containing a relatively large liquid volume, for example five litres or more, the hydraulic force exerted by the liquid during transport can break the bag, as is clearly explained in lines 34-50 of column 1 of US-A-4,968,624 which names the same inventors and the same proprietor as US-A-4,910,147.

For this reason US-A-4,968,624 describes a very complex rigid structure within which the bags containing the solutions have to be enclosed for their storage and transport.

Again for example, reference can be made to the method of using those sterile crystalline antibiotics (in powder form) contained in single-dose form in glass bottles sealed by rubber plugs. To make such antibiotics injectable into a patient by using a syringe a sterile solvent (water) is

(preferably high density polyethylene) or polyvinyl chloride, the intermediate layer is constructed of a barrier material (preferably aluminium), and the outer layer is constructed of polyolefin, nylon or polyester.

The packaging of the bag 1 in the bags 11 and 12 is known, and is of the type illustrated in US-A-4,700,838, corresponding to EP-B-201880.

The nature of the barrier material in its general terms (additional to aluminium) can be as defined in US-A-4,910,147.

When the sterile product in powder form is to be used, the bag 1 is removed from the protection bags, the ~~stopper~~ plug 8 is unscrewed, and into the port 2 a perfuser is inserted so that its free end 16 fractures the membrane 6 (Figure 4). The perfuser is a well known device and will not be described for simplicity. Its end sealedly engages the cavity in the appendix 2, through which the desired quantity of water can be easily fed under sterile conditions into the bag 1 to form with the powdered product a solution 17 which fills only a part of the bag capacity. This merely partial filling of the bag 1, not only is necessary to enable the liquid in the bag to be energetically shaken in order to quickly and completely dissolve ~~/ disperse or suspend/~~ the product in powder form to make it suitable for use, but it makes it possible to introduce into the bag the exactly controlled amount of liquid which is required for giving a solution in which the product is present at its predetermined concentration.
One of the preferred uses of the described bag is to preserve and transport sterile crystalline antibiotics and to form injectable solutions thereof (in hospitals and the like) in which the concentration of the antibiotics must be carefully controlled: this means that if the amount of an antibiotic closed in a bag is known, also the amount of water to be introduced into the same bag for forming the solution is known.
To give a detailed practical example, a bag 1 is prepared from a sheet of low density polyethylene of 150 micron thickness, the bag having a height of 35 cm and a width of 45 cm. 300 g of an antibiotic in powder form are fed into this bag and preserved in a sterile environment. The bag 1 is sealed within an intermediate bag of high density polyethylene of 100 micron thickness, having a height of 40 cm and a width of 48 cm. The intermediate bag is

then inserted into and sealed inside an outer bag of 43 cm height and 54.4 cm width formed from three layers joined together, the inner layer being formed of high density polyethylene of 0.075 mm thickness, the intermediate layer being formed of a sheet of aluminium of 0.01 mm thickness, and the outer layer being of polyester resin of 0.012 mm thickness.

When the antibiotic is to be used, the inner bag 1 is removed from the intermediate bag 11 and outer bag 12 and 3000 ml of injection-quality water are fed into it via the described perfuser (Figure 4) to form a solution of the required concentration for the particular therapeutic dose, in this case 100 mg/ml. It is important to note that the antibiotic solution 17 occupies only a part of the bag capacity to enable the antibiotic to be quickly and completely dissolved by vigorously shaking the bag. The bag capacity is preferably between 1.5 and 2 times the volume of the solution to be prepared in it.

The antibiotic solution obtained in this manner can be used directly, for example it can be transferred into sterile syringes each containing 30 ml of solution. The syringes can be filled in groups (for example 10, 20 or more syringes at a time) by automatic machines of known type which withdraw the solution through the free end 16 of the perfuser (by arranging the bag with the port 2 pointing downwards) used for feeding the liquid into the bag.

If desired, individual doses of the antibiotic solution can be withdrawn through the port 4 (the presence of which is not strictly necessary but is preferred). To do this, the ~~stopper~~ protection plug 9 is removed, and a rubber plug 20 (which seals that part of the cavity of the port 4 external to the bag 1) and the membrane 7 are perforated by the syringe needle.

When the syringe needle is removed, the solution is unable to flow from the bag 1, this being prevented by the rubber plug 20.

If the syringes are not used within a short time after their filling, they can be preserved in a freezer and then be despatched to the user in hospital in controlled temperature containers.

From the aforegoing description it is apparent that the antibiotic solution can be very easily and quickly formed at the desired concentration in a sterile environment, and that syringes can then be filled likewise easily and economically.

By proceeding in the aforedescribed manner, very important advantages are obtained compared with traditional systems in that it is no longer necessary to preserve the sterile antibiotic in powder form in glass bottles, a considerable reduction in the risk of contamination of the final pharmaceutical product is achieved (with the traditional system, for each syringe the solution has to be prepared individually and be fed into the syringe in environments which are generally not sterile), and there is a considerable cost and ecological saving consequent on the fact that it is no longer necessary to use glass bottles, metal rings, rubber plugs (one for each bottle), glass vials for solvents, etc.

All this leads to a considerable cost reduction, especially because a large number of specialized personnel are no longer required for preparing the individual antibiotic solutions, this being a very costly operation in hospitals or in those places in which a large quantity of antibiotic solutions has to be prepared.

Very considerable advantages are obtained even if the sterile products contained in the bags are not pharmaceutical products but are other products in powder form to be dissolved ~~/or dispersed/~~ in various liquids for their use. ~~/such as cell culture media./~~

In addition to the described bag, the invention also relates to the method for preserving and transporting sterile products in powder form and for dissolving ~~/or dispersing/~~ them in liquids under sterile conditions, as defined in the introductory part and in the claims accompanying this description.

ENCLOSURE 2

3A

drawn from a vial (which has firstly to be broken or opened), then the solvent is fed into the bottle by piercing its plug with the syringe needle, the bottle is shaken to dissolve the antibiotic powder, and the solution formed in this manner is drawn into the syringe through the needle which passes through the plug of the bottle, after which the solution can be injected into the patient.

Although this operation may be relatively simple to carry out by a user who has to prepare the solution and inject it only one or a few times a day, it becomes very demanding and costly in hospitals in which specialized personnel (nurses) have to repeat the same operation a very large number of times every day, with considerable time wastage, high cost and serious problems of maintaining sterility, these being enhanced by the need to dispose of a large number of empty glass bottles with rubber plugs, glass vials and miscellaneous packaging material.

Again it should be noted that it is not possible to prepare solutions of antibiotics (for example in bags such as those described in US-A-4,910,147 and in US-A-5,364,384) in suitable plants to then despatch them to hospitals, because such solutions remain unaltered only for a very short time, and then only if special care is taken for their preservation.

In order to solve the above mentioned problems the US-A-5,484,431 has proposed the use of a bag constructed from a flexible polyolefin material, sealed at its periphery and defining a closed sterile space containing a sterile solute or a

soluble product in powder form occupying only a minor portion of the capacity of the bag.

The bag has a plurality of ports through which a liquid can be introduced into it for dissolving the powder or solute and respectively for withdrawing the solution which has been formed within the bag.

According to the teachings of the US-A-5,484,431 the amount of liquid introduced into the bag is such to completely fill it as it is stated, for example, in line 62 of col. 8 and line 23 of col. 9 of the patent specification: in order to make it possible to dissolve the powder or solute contained therein, the bag must include internal means for creating turbulence within its interior (see lines 1-3 of col. 3): preferably the bag is provided with an internal seal 14 (see lines 43-45 and 56-60 of col. 4) which functions to create turbulence when the liquid flows into the bag ensuring an adequate mixing of the liquid and the powder or solute in order to create a solution.

Such solutions are for intravenous administration of dextrose solutions, saline, lactated Ringer's or the like whose concentrations in the respective solutions needs not to be exactly predetermined and the same in each bag.

The structure of the bag disclosed in the US-A-5,484,431 is not a simple one, because it must comprise internal means for creating turbulence within its interior as a consequence of the fact that the liquid introduced therein completely fills the bag, so that a simple shaking of the bag would practically be i AMENDED SHEET completely dissolve

3/3 3C

the powder or the solute. Moreover, since the bags are formed with flexible sheet of plastic materials and the bags are completely filled with the liquids introduced therein, it is impossible to obtain solutions all having the same preestablished concentration of the materials dissolved therein.

Finally, the solutions formed in the bags are used for intravenous administration, where it is not necessary to exactly control the amount of the active substances which are administered to the patients.

In the light of the aforegoing, the main object of this invention is to provide a bag of simple structure usable for preserving and transporting sterile products in powder form and for feeding into it a solvent to easily and quickly form a solution with predetermined concentration of the powdered product directly within the bag under sterile conditions, the bag being provided with at least one port through which the entire solution or a part thereof can be easily, quickly and safely withdrawn in order to be used, the volume of the solution being sufficiently large to supply a plurality of single individually usable doses of the same solution, for example for filling a plurality of syringes.

A further object is to provided a method which enables sterile products in powder form to be packaged in easily storable and transportable flexible bags, and further enables solutions with predetermined concentrations of such products to be subsequently easily and quickly formed directly within the bags which is to be used.

These and further objects are attained by a bag for preserving and transporting sterile products in powder form and for forming therein solutions with predetermined concentrations of said products, the bag being of polyolefins construction, being hermetically sealed at its periphery to define a sterile closed space and having at least one port also of polyolefin construction defining a passageway, the two ends of which open inside and respectively outside the bag, said passageway being closed by a pierceable membrane for the introduction of a solvent into the bag and respectively for the withdrawal of the solution therefrom, characterised in that each bag contains an amount of product in powder form adapt to give a solution with desired pre-determined concentration, that such a solution only partially fills the bag capacity, and in that the total amount of said solution is a multiple of single volumes of individual doses of the same solution

The invention concerns also a bag constructed of flexible polyolefin material and containing a ready to use solution prepared by introducing within a sealed bag originally containing a dosed amount of a soluble sterile product in powder form an amount of solvent adapt to give said ready to use solution with desired concentration of said product, characterised in that the bag capacity is such that it is

only partially filled by said ready to use solution, and in that the total volume of said solution is a multiple of single volumes of individual doses of the same solution.

Finally, the invention concerns a method for preparing solutions with predetermined concentrations of soluble sterile products in powder form enclosed and sealed within sterile bags constructed of flexible polyolefin materials, characterised in that a bag containing a dosed amount of soluble sterile product in powder form adapt to give a solution of predetermined concentration is fed with an amount of solvent adapt to give a ready to use solution with desired concentration of the product, in that the bag capacity is such that it is only partially filled by said solution, and in that the volume of the solution suffices to supply a plurality of single individual doses of the same solution.

The bag structure and its method of use will be more apparent from the ensuing description of a preferred embodiment thereof given by way of non-limiting example with reference to the accompanying drawings, on which:

Figure 1 is a schematic front view of the bag, of which
Figure 2 show an enlarged partial section coplanar with that portion of the bag on which the bag access port is provided;
Figure 3 is a section through the bag taken on the line 3-3 of Figure 1, the bag being shown filled only to a minimum extent with a product in powder form and with the port closed;
Figure 4 is similar to Figure 3, but with the port open for feeding into the bag a liquid having a volume occupying only a part of the bag capacity; and
Figure 5 shows the closed bag inserted into a further two bags used for its storage and its despatch to the powdered product user.

Reference will firstly be made to Figures 1 to 4, which show a bag 1 constructed of polyolefin, preferably low density polyethylene, sealed hermetically along its entire periphery and having at one end a port 2 formed in one piece with and projecting from an elongate tapered body 3 from which there projects a further port

ENCLOSURE 1

Claims:

1. A bag for preserving and transporting soluble sterile products in powder form and for forming therein solutions with predetermined concentrations of said products, the bag being of poyolefin construction, being hermetically sealed at its periphery to define a sterile closed space and having at least one port also of polyolefin construction defining a passageway the two ends of which open inside and respectively outside the bag, said passageway being closed by a pierceable membrane for the introduction of a solvent into the bag and respectively for the withdrawal of the solution therefrom, characterised in that each bag contains an amount of product in powder form adapt to give a solution with desired predetermined concentration, that such solution only partially fills the bag capacity, and in that the total volume of said solution is a multiple of single volumes of individual doses of the same solution.

2. A bag according to claim 1, characterized in that the amount of product in powder form enclosed within each bag is such that the bag capacity is between 1.5 and 2 the volume of the solution with predetermined concentration of such product.

3. A bag constructed of flexible polyolefin material and containing a ready to use solution prepared by

introducing within a sealed bag originally containing a dosed amount of a soluble sterile product in powder form an amount of solvent adapt to give said ready to use solution with desired concentration of said product, characterized in that the bag capacity is such that it is only partially filled by said ready to use solution, and in that the total volume of said solution is a multiple of single volumes of individual doses of the same solution.

4. A bag according to claim 3, characterized in that the bag capacity is between 1.5 and 2 times the volume of the solution formed therein.

5. A method for preparing solutions with predetermined concentrations of soluble sterile products in powder form enclosed and sealed within sterile bags constructed of flexible polyolefin materials, characterized in that a bag containing a dosed amount of soluble sterile product in powder form adapted to give a solution of predetermined concentration is fed with an amount of solvent adapt to give a ready to use solution with desired concentration of the product, in that the bag capacity is such that it is only partially filled by said solution, and in that the volume of the solution suffices to supply a plurality of single individual doses of the same solution.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

FRIGNOLI, Luigi
Ing. A. Giambrocono & C. s.r.l.
Via Rosolino Pilo, 19/B
I-20129 Milano
ITALIE

Date of mailing (day/month/year) 18 June 1999 (18.06.99)	
Applicant's or agent's file reference G67708 LF/mg	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/02745	International filing date (day/month/year) 23 April 1999 (23.04.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 20 October 1998 (20.10.98)
Applicant ACS DOBFAR S.P.A. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
20 Octo 1998 (20.10.98)	MI98A002256	IT	03 June 1999 (03.06.99)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

P. Regis

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:
FRIGNOLI, Luigi
Ing. A. Giambrocono & C. s.r.l.
Via Rosolino Pilo, 19/B
I-20129 Milan
ITALIE

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year)	
27 April 2000 (27.04.00)	
Applicant's or agent's file reference G67708 LF/mg	**IMPORTANT NOTICE**
International application No. PCT/EP99/02745	**International filing date** (day/month/year) 23 April 1999 (23.04.99) — **Priority date** (day/month/year) 20 October 1998 (20.10.98)
Applicant ACS DOBFAR S.P.A. et al	

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,EP,ES,FI,GB,GE,GH,GM,HR,HU, ID,IL,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD, SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   27 April 2000 (27.04.00) under No. WO 00/23036

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
G67708 LF/mg		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 02745	23/04/1999	20/10/1998
Applicant		
ACS DOBFAR S.P.A		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 5

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
F[redacted]P 99/02745

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61J1/00 A61J1/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61J C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 484 431 A (SCHARF MIKE ET AL) 16 January 1996 (1996-01-16)	1,2
A	column 1, line 11 - line 15 column 1, line 39 -column 2, line 6 column 2, line 15 - line 60 column 4, line 4 - line 23 column 4, line 61 -column 6, line 21; figures	4

X	US 4 282 863 A (BEIGLER MYRON A ET AL) 11 August 1981 (1981-08-11)	1,2
A	column 1, line 8 - line 13 column 7, line 20 - line 51; claim 7; figures	4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 1999	19/10/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Baert, F

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]EP 99/02745

C.(Continuation) DOCUMENTS CONSIDER[redacted]TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 385 564 A (SLATER GLENN L ET AL) 31 January 1995 (1995-01-31)	1,2
A	abstract column 4, line 4 -column 5, line 9; figures 2,3	4
A	US 5 364 384 A (GRABENKORT RICHARD W ET AL) 15 November 1994 (1994-11-15) column 3, line 21 - line 41; figures	1
A	US 4 700 838 A (FALCIANI MARCO ET AL) 20 October 1987 (1987-10-20) cited in the application the whole document	3
A	US 4 968 624 A (BACEHOWSKI DAVID ET AL) 6 November 1990 (1990-11-06) cited in the application abstract; claims; figures	1
A	US 4 910 147 A (BACEHOWSKI DAVID V ET AL) 20 March 1990 (1990-03-20) cited in the application abstract; claims; figures	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
P EP 99/02745

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